Effect of Aluminum Hydroxide, an Antacid, on the Pharmacokinetics of New Quinolones in Humans

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Summary

Effect of aluminum hydroxide on the pharmacokinetics of new quinolones, ofloxacin, enoxacin and norfloxacin, was investigated in cross-over study using five healthy male volunteers. Serum levels of the three drugs were decreased significantly up to 10 hours later by the concurrent administration of aluminum hydroxide. C_{max} and AUC of the respective drug were decreased significantly by combined administration with aluminum hydroxide. Urinary excretion rates of the drugs within 24 hours were also decreased significantly by the concurrent administration of aluminum hydroxide. This combination effect of aluminum hydroxide on the pharmacokinetics of new quinolones was largest in case of norfloxacin and smallest in ofloxacin. Thus, these results suggest that the combination effect of aluminum hydroxide may be induced by the inhibition of absorption of new quinolones in the gastrointestinal tract.

Introduction

Since the introduction of new quinolones for the chemotherapy of various infectious diseases in humans, their untoward adverse reactions as well as excellent chemotherapeutic efficacy have been reported. With respect to drug interactions among these adverse reactions, first, the interaction of new quinolones with theophylline has been noticed in the therapy of asthmatic patients (1, 2). In addition, as another type of new quinolone interaction, it has been reported recently that antacids including aluminum hydroxide have a profound influence on the oral absorbability of ofloxacin and ciprofloxacin (3-8). Aluminum hydroxide has been prescribed frequently for the suppression of symptoms of the gastrointestinal tract such as nausea and vomiting which have been shown to be major among untoward adverse reactions of new quinolones (9). However, it remains unknown whether or not the concurrent oral administration of aluminum hydroxide induces a significant effect on the oral absorbability of new quinolones excepting ofloxacin and ciprofloxacin. Accordingly, it is of great importance to investigate the relative potency of the interaction of new quinolones with aluminum hydroxide for the clinical use of the drugs. Therefore, effects of concurrent administration of aluminum hydroxide on the pharmacokinetics of new quinolones, ofloxacin, enoxacin and norfloxacin, were compared in cross-over study in healthy male volunteers.

This paper describes the comparison of the combination effect of aluminum hydroxide on pharmacokinetic parameters and urinary excretion of the three drugs in humans.

Materials and Methods

Subjects

Five male healthy volunteers weighing 50-71 kg and being 30-45 years of age were used in the study. A physical examination, including clinical and hematological laboratory examinations was performed during the week prior to dosing. Subjects exhibiting evidence of organic disease were excluded from the study.

Formulations

The formulations of new quinolones, tablets, lot No. 3 QPT-11, lot No. N 5 X 5350 and lot No. 3711, containing 100 mg of ofloxacin (Daiichi Seiyaku Co., Ltd., Tokyo, Japan), norfloxacin (Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan) and enoxacin (Dainippon Pharmaceutical Co., Ltd., Osaka, Japan), respectively, were used in the study.

The formulation of antacid, granule, lot No. BII 307, containing 999 mg of aluminum hydroxide (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) in 1 g was used in the study.

Protocol

The subjects received a single oral dose of 200 mg (2 tablets) of the drugs with or without 1 g of aluminum hydroxide granule with 100 ml water under fasting. After dosing, samples of blood and urine were taken at various time intervals. This study was carried out in cross-over method using the same five subjects. Washout period of each drug was one week.

Measurements

Quantitation of new quinolones in the serum and urine was carried out by disc agar

diffusion microbiological method using *Escherichia coli* Kp or *Bacillus subtilis* ATCC 6051 as indicator organisms.

Calculations

Pharmacokinetic parameters of the drugs were calculated according to one compartment open model.

Statistical analysis was performed by paired Student t-test.

Results

Effect of combined administration of aluminum hydroxide on serum concentrations of new quinolones

As shown in figure 1, serum concentrations of ofloxacin, enoxacin and norfloxacin were decreased significantly up to 10 hours after dosing together with aluminum hydroxide.

By co-administration of aluminum hydroxide, serum concentrations of ofloxacin, enoxacin and norfloxacin at 1 hour after dosing were decreased from 2.85, 2.13 and 1.40 $\mu\text{g/ml}$ to 1.04, 0.32 and <0.10 $\mu\text{g/ml}$, respectively. Thus, decrease in the serum concentrations of norfloxacin was extremely large, while decrease in the serum concentrations of ofloxacin was small.

Table I shows the results of effect of aluminum hydroxide on pharmacokinetic parameters of ofloxacin, enoxacin and norfloxacin in human subjects. C_{max} values of ofloxacin, enoxacin and norfloxacin were decreased significantly from 3.23, 2.26 and 1.45 $\mu\text{g/ml}$ to 1.31, 0.46 and <0.1 $\mu\text{g/ml}$, respectively, by combination with aluminum hydroxide. $\text{AUC}_{0-24\text{h}}$ values of ofloxacin, enoxacin and norfloxacin were decreased significantly by 52.1%, 15.4% and 2.7% by the concurrent administration of aluminum hydroxide. In addition, T_{max} of

Fig. 1. Effect of the combined administration of aluminum hydroxide on serum concentrations of new quinolones in human subjects.

The subjects received a single oral dose of 200 mg of new quinolones with or without 1 g of aluminum hydroxide with 100 ml water under fasting. Vertical bars represent standard deviation. ○ : new quinolone alone. ● : new quinolone with aluminum hydroxide. * $p < 0.05$, ** $p < 0.01$, § $p < 0.001$: significantly different from new quinolone alone.

Table I. Effect of aluminum hydroxide on pharmacokinetic parameters of ofloxacin, enoxacin and norfloxacin in human subjects

Group	Cmax ($\mu\text{g/ml}$)	Tmax (h)	T _{1/2} (h)	AUC _{0-24h} ($\mu\text{g} \cdot \text{h/ml}$)
Ofloxacin	3.23 $\pm$ 0.55	1.10 $\pm$ 0.55	5.08 $\pm$ 0.76	23.8 $\pm$ 4.65
Ofloxacin + AL	1.31 $\pm$ 0.53*	2.40 $\pm$ 1.52	6.03 $\pm$ 2.21	12.4 $\pm$ 4.82*
Enoxacin	2.26 $\pm$ 0.38	0.80 $\pm$ 0.27	3.89 $\pm$ 0.97	11.4 $\pm$ 0.74
Enoxacin + AL	0.46 $\pm$ 0.39§	1.60 $\pm$ 1.48	ND ^{a)}	1.76 $\pm$ 1.45§
Norfloxacin	1.45 $\pm$ 0.24	1.20 $\pm$ 0.45	2.91 $\pm$ 0.31	6.73 $\pm$ 1.39
Norfloxacin + AL	<0.1§	ND	ND	0.18 $\pm$ 0.41§

Each value represents the mean $\pm$ standard deviation for 5 subjects. AL=aluminum hydroxide. The subjects received a single oral dose of 200 mg of new quinolones with or without 1 g of aluminum hydroxide with 100 ml water under fasting. * $P < 0.05$, § $P < 0.001$: significantly different from new quinolone alone. a) Not detected.

Table II. Effect of aluminum hydroxide on cumulative urinary excretion of ofloxacin, enoxacin and norfloxacin in human subjects

Group	Cumulative urinary excretion (% of dose) by			
	2 h	4 h	8 h	24 h
Ofloxacin	16.4 $\pm$ 5.76	31.4 $\pm$ 5.93	54.3 $\pm$ 6.91	87.0 $\pm$ 4.29
Ofloxacin + AL	7.47 $\pm$ 2.97*	19.0 $\pm$ 11.1	34.5 $\pm$ 17.5*	55.7 $\pm$ 22.9*
Enoxacin	18.5 $\pm$ 4.59	29.7 $\pm$ 5.06	43.6 $\pm$ 5.05	59.4 $\pm$ 4.37
Enoxacin + AL	5.14 $\pm$ 6.06**	10.2 $\pm$ 9.09§	15.3 $\pm$ 11.2§	21.6 $\pm$ 12.8§
Norfloxacin	12.0 $\pm$ 3.85	22.4 $\pm$ 7.15	31.4 $\pm$ 9.96	40.2 $\pm$ 11.92
Norfloxacin + AL	1.12 $\pm$ 1.12**	2.28 $\pm$ 2.39§	3.31 $\pm$ 3.52§	4.55 $\pm$ 4.56§

Each value represents the mean $\pm$ standard deviation for 5 subjects. AL=aluminum hydroxide. The subjects received a single oral dose of 200 mg of new quinolones with or without 1 g of aluminum hydroxide with 100 ml water under fasting. * $P < 0.05$, ** $P < 0.01$, § $P < 0.001$: significantly different from new quinolone alone.

the drugs was prolonged by approximately 2 times.

Thus, the combination effect of aluminum hydroxide on the pharmacokinetic parameters of new quinolones was largest in norfloxacin, moderate in enoxacin, and smallest in case of ofloxacin.

The results of the effect of co-administration of aluminum hydroxide on the cumulative urinary excretion of the three drugs are given in table II. Co-administration of aluminum hydroxide produced the suppression of the urinary excretion of the three drugs from 2 hours after dosing. At 24 hours later, urinary excretion rates of ofloxacin, enoxacin and norfloxacin were decreased significantly from 87.0%, 59.4% and 40.2% of the dose to 55.7%, 21.6% and 4.55% of the dose, respectively, indicating that the influence of co-administration of aluminum hydroxide on urinary excretion of new quinolones was extremely large in norfloxacin, and small in ofloxacin.

Discussion

In the present study, we compared the combination effect of aluminum hydroxide, an

antacid, on the pharmacokinetics of new quinolones in the cross-over study using the same healthy subjects in order to determine the relative potency in the interaction of new quinolones with the antacid. First, the present study has elucidated that this interaction with aluminum hydroxide is observed in all the new quinolones tested including ofloxacin. With respect to the mechanism of the interaction of new quinolones with aluminum hydroxide, Tachizawa et al (10) have clarified that the combination effect of aluminum hydroxide may be caused by the inhibition of the intestinal absorption of new quinolones through the chelate formation of the drugs with Al^{3+} ions released from aluminum hydroxide in the gastric juice.

Next, the present study has also clarified that the combination effect of aluminum hydroxide on the pharmacokinetic parameters and urinary excretion rates is largest in norfloxacin, moderate in enoxacin, and smallest in case of ofloxacin, thus indicating that the lower the oral absorbability of new quinolones (11-13) is, the larger the combination effect of aluminum hydroxide appears. In the case of ofloxacin, there actually seems no problem in the clinical use of the drug combined with aluminum hydroxide, because peak serum concentration (C_{max}) after oral administration of 200 mg of the drug in combination with aluminum hydroxide exceeded considerably the range of MIC_{90} values reported in many Gram-positive and -negative organisms (9), even if, in this study, the C_{max} value was decreased to $1.31 \mu\text{g/ml}$ by co-administration of the antacid. In fact, Maesen et al (8) have shown that there exist no significant differences in the serum and sputum concentrations of ofloxacin and in its clinical effectiveness between patients with acute purulent exacerbations of chronic bronchitis receiving 600 mg ofloxacin with one tablet of Maalox (the formulation containing 400 mg $\text{Mg}(\text{OH})_2$ and 200 mg $\text{Al}(\text{OH})_3$) and receiving ofloxacin alone. On the contrary, the serum concentrations of norfloxacin after oral administration of 200 mg of the drug in combination with aluminum hydroxide were extremely reduced to less than $0.1 \mu\text{g/ml}$ throughout the experimental periods, and below the range of MIC_{90} values reported in Gram-positive and -negative organisms (9). Therefore, it is clear that an appropriate attention must be paid to the combination of norfloxacin with aluminum hydroxide in order to maintain the effectiveness of norfloxacin in its clinical use. Accordingly, further clinical studies on the detailed dosage regimens for the combination of new quinolones with aluminum hydroxide may be required for the effective treatment of patients with various infectious diseases.

Thus, it is concluded from the present results that the pharmacokinetic interaction of new quinolones with aluminum hydroxide may be induced by the inhibition of the gastrointestinal absorption of new quinolones by the antacid.

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